PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 12 December 2000 (12.12.00)	
International application No. PCT/FI00/00260	**Applicant's or agent's file reference** ÅP2911
International filing date (day/month/year) 29 March 2000 (29.03.00)	**Priority date** (day/month/year) 15 April 1999 (15.04.99)
Applicant KOULU, Markku et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   29 September 2000 (29.09.00)

   [ ] in a notice effecting later election filed with the International Bureau on:

   _____

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer F. Baechler
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

FI0000260

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 00/00260

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C12Q 1/68 // A61P 009/10
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NATURE MEDICINE, Volume 4, No 12, December 1998, Matti K. Karvonen et al, "Association of a leucine(7)-to-proline(7) polymorphism in the signal peptide of neuropeptide Y with high serum cholesterol and LDL cholesterol levels" page 1434 - page 1437	1-2,4-7, 12-13
Y	--	3,8-11,12-13
Y	CLINICAL SCIENCES, Volume 114, 1996, Emily Y. Chew et al, "Association of Elevated Serum Lipid Levels With Retinal Hard Exudate in Diabetic Retinopathy" page 1079 - page 1084	3-4,8-11, 12-13
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[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 Sept 2000	25 -09- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Patrick Andersson/ELY Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 00/00260

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DIABETES, Volume 45, No 3, June 1996, Hideki Ito et al, "Risk Factor Analyses for Macrovascular Complication in Nonobese NIDDM Patients" --	3-4,8-11, 12-13
A	Diabetes Research and Clinical Practise, Volume 21, 1993, Hiroo Ueda et al, "Importance of serum cholesterol level in development of diabetic autonomic neuropathy" page 123 - page 126 --	3-4,8-11, 12-13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI00/00260

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-3 and 4-11
because they relate to subject matter not required to be searched by this Authority, namely:

see extra sheet *

2. ☒ Claims Nos.: 4-6
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see extra sheet **

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

see extra sheet ***

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI00/00260

continuation of box I

*

Claims 1-3 relates to a diagnostic method and claims 4-11 a method of treatment of the animal or human body by therapy. See PCT Rule 39(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects.

**

Claims no. 4-6 relates to treatment of atherosclerosis using agents effecting polymorphic prepro-NPY signal peptides, the description or the claims does not give any examples of such agents, moreover they could be agents known for treatment of atherosclerosis. Therefore, the claims is not considered to comply with PCT article 5(disclosure) or PCT article 6 (clarity).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI00/00260

continuation of box II

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According to PCT rule 13.2, an international application shall relate to one invention only or a group of inventions linked by one or more of the same or corresponding "special technical features", i.e. features that define a contribution which each of the inventions considered as a whole makes over the prior art.

The claimed invention relates to a method of diagnosis of susceptibility for having an increased risk of either atherosclerosis or diabetic retinopathy. In the method polymorphism in the signal peptide part of prepro- neuropeptide Y (NPY) is detected.

Special technical features unifying the methods of diagnosing atherosclerosis or diabetic retinopathy could be:
1. detection of polymorphism in prepro-NPY signal peptide or,
2. some link between atherosclerosis and diabetic retinopathy, making diabetic retinopathy a subgroup of different states developed together with, or as a consequent of, atherosclerosis.

In Karvonen MK et al, see search report, polymorphism in the signal peptide part NPY is associated with high levels of total cholesterol and LDL. High levels of total and LDL cholesterol are important risk factors in the development of atherosclerosis. It is evident from Karvonen et al, that a person having a mutation in the signal peptide part of NPY is susceptible for an increased risk of atherosclerosis. Consequently, technical feature 1 is known through Karvonen thus disqualified as a unifying feature, technical feature 2 disqualifies as well since the association between NPY polymorphism and atherosclerosis is considered evident. No other possible technical feature has been found.
Consequently, the following inventions have been found:

Invention 1, claims 1-2, 4-7 completely, 12-13 partially methods for diagnosing, treating and screening related to atherosclerosis

Invention 2, claims 3-4, 8-11 completely, 12-13 partially methods for diagnosing, treating and screening related to diabetic retinopathy.

An additional fee was paid. Both inventions have been searched.

PATENT COOPERATION TREATY

PCT

REC'D 31 JUL 2001
WIPO

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference AP2911	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/FI00/00260	International filing date *(day/month/year)* 29.03.2000	Priority date *(day/month/year)* 15.04.1999
International Patent Classification (IPC) or national classification and IPC7 C 12 Q 1/68 // A 61 P 9/10		
Applicant Hormos Medical OY LTD et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29.09.2000	24.07.2001
Name and mailing address of the IPEA/SE [illegible] Tele: 17978 PATOREG-S	Authorized officer Hampus Rystedt/BS
Facsimile No. 08-667 72 88	Telephone No. 08-782 25 00

Form PCT/IPEA/409 (cover sheet) (January 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FI00/00260

I. Basis of the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed

☐ the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the claims:
pages _____, as originally filed
pages _____, as amended (together with any statement) under article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the drawings:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheet/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2 (c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FI00/00260

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 4-11

because:

☒ the said international application, or the said claims Nos. 4-11
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

Claims 4-11 relate to methods for treatment of of the animal or human body by therapy, which this IPEA is not required to examine. See PCT Rule 67.1 (iv).

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 4-6, 8-10
are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 4-6 and 8-10 relate to treatment of atherosclerosis (4-6) or diabetic retinopathy (8-10) using agents affecting polymorphic preproNPY signal peptides. The description or the claims do not give any examples of such agents; moreover they could be agents known for treatment of atherosclerosis or diabetic retinopathy. Therefore, the claims are not considered to comply with PCT article 5 (sufficient disclosure) or PCT article 6 (clarity).

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☒ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
- ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☒ all parts.
- ☐ the parts relating to claims Nos. _____

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-3,12,13	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-3,12,13	NO
Industrial applicability (IA)	Claims	1-3	YES
	Claims	12,13	NO

2. Citations and explanations (Rule 70.7)

The present application relates to the use of a polymorphism in the signal peptide of a precursor of human Neuropeptide Y, preproNPY, more specifically the substitution of position 7 leucine for proline. The polymorphism is indicative of increased risk for development of atherosclerosis and diabetic retinopathy. A correction of the polymorphism, i.e. reverting position 7 to leucine, could reduce this same risk.

The following documents are considered relevant:
D1: Karvonen, M.K. et al, Association of a leucine(7)-to-proline(7) polymorphism in the signal peptide of neuropeptide Y with high serum cholesterol and LDL cholesterol levels, Nature Medicine, 1998, vol 4, pp 1434-1437
D2: Chew, E.Y. et al, Association of Elevated Serum Lipid Levels With Retinal Hard Exudate in Diabetic Retinopathy, Clinical Sciences, 1996, vol 114, pp 1079-1084

D1, cited in description as reference 15, describes the Leu(7)Pro polymorphism in preproNPY and states that it is associated with high levels of LDL and total cholesterol levels, see the abstract. The abstract also mentions that high LDL and total cholesterol levels are important risk factors in the development of atherosclerotic coronary artery disease. It is therefore considered obvious to a person skilled in the art that the Leu(7)Pro polymorphism may be used for assesing an increased risk of atherosclerosis, and also that this risk may be reduced by counteracting the polymorphism or its effects. Claims 1 and 2 are consequently considered to lack inventive step.

.../...

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

The use of animal models for studying the effects of the Leu(7)Pro polymorphism is also considered to be obvious to the person skilled in the art. It has not been shown that the methods using animal models according to claims 12 and 13 actually work. They are consequently considered to both lack inventive step and industrial applicability.

D2 describes the association of elevated LDL and total cholesterol levels with retinal hard exudate, which constitutes a part of the condition diabetic retinopathy. Given this information it is not considered inventive to use the polymorphism described in D1 also for assesing the risk for diabetic retinopathy. Claim 3 is therefore not considered inventive.